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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,060	01/04/2002	Andrew Koff	14538A-005111US	5760
20350	7590	07/28/2004	EXAMINER	
TOWNSEND AND TOWNSEND AND CREW, LLP TWO EMBARCADERO CENTER EIGHTH FLOOR SAN FRANCISCO, CA 94111-3834			SHUKLA, RAM R	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/038,060

Applicant(s)

KOFF ET AL.

Examiner

Ram R. Shukla

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 May 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9/3/02 6) ☐ Other: _____

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DETAILED ACTION

1. Applicants' response and amendments filed 5/10/04 have been received and entered.
2. Claims 1-11 are pending and under consideration.

Specification

The objection to the specification regarding the description of various figures is maintained for reasons of record set forth in the previous office action of 11/7/03. It is noted that the applicants failed to respond to the objection in their response to the office action of 11/7/03.

For any response to be fully responsive to this office action, applicants are required to respond to the objection and correct the error in the specification.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-11 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the proliferation of thymocytes in a transgenic mouse, comprising altering the endogenous gene encoding p27kip1 of the mouse in the somatic and germ cells of the transgenic mouse, wherein the transgenic mouse does not produce a functional p27kip1, wherein the p27kip gene is altered by inserting a nucleotide sequence encoding a positive selectable maker in the endogenous p27kip1 gene, mutation or deletion of the endogenous p27kip1 gene, wherein the transgenic mouse is produced by introducing a plasmid in mouse ES cells and injecting the mouse embryonic ES cells into a blastocyst stage embryo, wherein the plasmid comprises, a p27kip1 gene altered by inserting the nucleotide sequence encoding the positive selectable

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marker and a nucleotide sequence encoding a negative selectable marker such that the distance between the nucleotide sequence encoding the negative selectable marker and the p27kip1 gene allows homologous recombination between the altered p27kip1 gene in the plasmid and the endogenous p27kip1 gene present in the genome of the mouse ES cells, does not reasonably provide enablement for other embodiments of the claimed invention for reasons of record set forth in the previous office action of 11/7/03. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is noted that applicants amended claim 1 by replacing the term "a somatic cell" to "a thymocyte, or a multipotent cell that differentiates into a thymocyte." Claim 2 has been amended to recite that "the multipotent cell is a bone marrow cell". The amended claims would encompass altering an endogenous gene encoding p27kip1 in a thymocyte or bone marrow in vivo in any non-human animal and therefore all the issues of enablement discussed in the previous office action of 11/7/03 would be applicable.

Response to Arguments

Applicant's arguments filed 5/10/04 have been fully considered but they are not persuasive. Regarding applicants' arguments of examiner's initial burden of providing evidence, it is emphasized that the office action has dealt in detail all the issues based on sound scientific reasoning, state of the art and the disclosure. It is emphasized in the beginning that the specification teaches a transgenic mouse in which endogenous p27kip1 gene has been knocked out and that this method cannot be broadly used to alter an endogenous p27kip1 gene in a thymocyte or any multipotent cell in any non-human animal in vivo for reasons of record set forth in the previous office action of 11/7/03. Applicants' arguments that present invention is based on surprising discovery that thymocyte proliferation can be increased by inhibiting p27kip1 function is not sufficient for the claimed method to be enabled in light of the specification and state of the art of record. In view of applicants

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submission that applicants invention does not encompass inhibit p27kip1 gene using antibody, the rejection pertaining to this issue is withdrawn. Applicants' arguments that the claims do not recite any particular threshold for targeting specificity or of clinical therapeutic efficacy are not persuasive because eventhough claims do not recite such a limitation, intended use of the claimed method is for treatment and therefore, claimed are broadly interpreted to encompass such limitation. Applicants' argue on page 7 (item C):

"Applicants believe that the Examiner's reliance on Miller is misplaced. Miller discusses targeted vectors for gene delivery in the context of therapeutic efficacy. Miller does not state that currently available delivery systems are ineffective, but simply reviews how such systems "can be manipulated to improve their targeting to specific cell types." Abstract (emphasis added)."

In response it is noted that applicants have ignored the entire discussion of the Miller article and emphasized one sentence of the abstract and even if one has to take that sentence at its face value, the specification does not teach how to manipulate vectors for improving their targeting.

Regarding applicants arguments in item D on page 7, it is noted that the intended use for the claimed method was interpreted to be for in vivo and ex vivo therapy. Applicants have not provided any evidence or argument that their claimed invention is not drawn to therapy and therefore, their arguments are misplaced and irrelevant. If applicants argue that the intended use is not for therapy, applicants are to provide evidence as to what is (are) the intended use for the claimed method and the support in the specification. It is emphasized that the examiner presented evidence based on sound scientific reasoning to support the enablement rejection and the applicants have not provided any evidence to rebut the rejection, except for statements which are not supported by any evidence.

Finally, in item F on page 8, applicants argue that ES cells and ES like cells had been identified and isolated from various species and list several articles. First applicants did not provide any of these articles, therefore the content of these articles cannot be considered. Additionally, all these articles modified methods for

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their own application and none of these articles argue that culturing, maintaining and transgenesis based on ES cells was routine and predictable at the time of the invention. Contrary to this, the articles cited by the Examiner in the rejection supported that the basis of rejection. It is reiterated that the examiner presented evidence based on sound scientific reasoning to support the enablement rejection and the applicants have not provided any evidence to rebut various issues of the enablement rejection, except for statements which are not supported by any evidence. Applicants' arguments alone cannot take place of evidence lacking in the record (see *In re Scarbrough* 182 USPQ, (CCPA) 1979).

5. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record set forth in the previous office action of 11/7/03.

Response to Arguments

Applicant's arguments filed 5/10/04 have been fully considered but they are not persuasive. Regarding the written description rejection, applicants argue:

"In the present case, independent claim 1 recites a "method for increasing the proliferation of thymocytes in a non-human animal comprising altering an endogenous gene encoding p27kip1 in a thymocyte, or a multipotent cell that differentiates into a thymocyte, of the animal to cause a functional deficiency of cyclin-dependent kinase inhibitor function of p27kip1, thereby increasing the proliferation of thvmocvtes in the animal" (emphasis added). It is noted that claim 1 does not recite any other effect of altering p27kip1 other than increasing the proliferation of thymocytes. Thus, any other phenotypic effects of p27kip1 inhibition are irrelevant to the question of written description."

However, these arguments are not persuasive because in view of the unpredictability of making transgenic non-human animals, the effect of altering the

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expression of an endogenous p27kip1 gene can not be predicted and therefore an artisan would not know what would be the phenotype of the animals produced by the claimed method. Again applicants did not provide any evidence except for arguments and as discussed before, Applicants' arguments alone cannot take place of evidence lacking in the record (see *In re Scarbrough* 182 USPQ, (CCPA) 1979).

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 4-8 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record set forth in the previous office action 11/7/03 .

In view of applicants' arguments, 112 second paragraph rejection of claims 1 and 9 has been withdrawn.

Applicants arguments regarding claim 4 are not persuasive. Applicants quote *Molecular Cloning: A Laboratory Manual* to describe what is meant by a selectable marker. However, applicants seem to ignore that the Sambrook et al says "selectable markers encoded by the plasmid" which clearly encodes that selectable marker is a protein that is encoded by a plasmid and no such limitation is present in the instantly presented claim. Modifying the claim to recite, for example, "by insertion of nucleotide sequences encoding a positively selectable marker" will be remedial.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. Claims 1-11 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Roberts JM et al (US Patent No 5,958,769, dated 8-28-99, filing date 1-18-1996) for reasons of record set forth in the previous office action of 11/7/03.

Response to Arguments

Applicant's arguments filed 5/10/04 have been fully considered but they are not persuasive. Applicants have asserted that the invention is not anticipated by Robert et al in view of a declaration under 37 CFR 1.131, however, no such declaration has been submitted and therefore the rejection is maintained.

10. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is

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(571) 272-0735 . The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for TC 1600 is (703) 872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (571) 272-0532.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ram R. Shukla, Ph.D.
Primary Examiner
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A handwritten signature in black ink, appearing to read 'mshukla', with a horizontal line drawn underneath it.

**RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER**